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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,436	07/16/2001	Hermann Wagner	C1041/7010	1340

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,436	WAGNER ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *104-110 and 112-114* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *104-110,112-114* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 104-110 and 112-114 are pending.

Applicant's traversal, and the amendment to claims 104 and 108 filed on 6/7/06 is acknowledged and considered by the examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 104-110 and 112-114 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 104-110 and 112-114, as best understood, are readable on a genus of oligonucleotides 10-50 nucleotide long comprising a sequence chosen from GGGGG, GAGGG, GGGAG, GTGGG, and GGGTG, wherein the oligonucleotide does not comprise a CG dinucleotide to treat tumor in a subject, wherein the genus of oligonucleotides is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates a genus of poly G motifs to co-stimulate cytotoxic T-lymphocytes (CTLs) or natural killer cells (abstract). The claims are directed to using a genus of oligonucleotides with a tumor specific antigen to treat a vertebrate subject having a tumor. The skilled artisan understands that genus reads on antisense, aptamers, oligomer, etc.. There is a variation among species embraced by the claimed genus. For example, the prior art teaches using G-rich oligo aptamers for inhibiting an immune response (WO 98/29430, cited on a PTO-1449). The instant specification does not specifically disclose making and/or using a tumor specific antigen and an oligonucleotides 10-50 nucleotide long comprising a sequence chosen from GGGGG, GAGGG, GGGAG, GTGGG, and GGGTG, wherein the oligonucleotide does not comprise a CG dinucleotide to treat tumor in a subject. The instant specification discloses an oligonucleotide (PZ2, SEQ ID NO: 2) with IL-2 co-stimulates T cells in vitro (Example 7) and PZ2 co-stimulates natural killer cells in vitro (Example 8). The specification further discloses that only single stranded PZ1 (SEQ ID NO: 1), PZ2 (SEQ ID NO: 2), and PZ3 (SEQ ID NO: 3), but not double stranded PZ1, PZ2, and PZ3 co-stimulate T cells in vitro. The specification further discloses:

> To analyze the effects of ODN on T cells a costimulation assay was used. In this assay purified T cells are stimulated via their TCR (signal 1). This signal is not sufficient to induce cytokine secretion and subsequent T cell growth (see Figure 9A). Addition of exogenous IL-2 demonstrate that signal 1 is operative. ODN by itself have no stimulatory activity on T cells alone. If however T cells receive a signal via

> their TCR they become sensitive to ODN. ODN provide to these T cells a potent second signal that induces cytokine secretion (Figure 9B) and T cell growth (Figure 9A). The results demonstrate that G-motif ODN-costimulated anti-cD3 triggered T cells in a sequence and concentration dependent fashion. The analyses allowed the definition of the minimal ODN motif effective for T cell costimulation. Page 31.

One skilled in the art can envision a sequence with the claimed structure, but would be unable to determine without further experimentation if the sequence had a function that was considered essential for the claimed genus of oligonucleotides. Furthermore, the specification does not disclose how to make a sufficient number of species to represent the genus of claimed oligonucleotides.

The mere contemplation of the claimed genus in the specification is not sufficient to support the present claimed invention directed to a genus of oligonucleotides comprising four contiguous guanines. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of oligonucleotides that must possess the biological properties as contemplated by applicants' disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would

recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of oligonucleotides that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 104-110 and 112-114 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims read on using a genus of oligonucleotides comprising a G motif for *in vivo* administration to a genus of vertebrate subjects to treat a genus of tumors. Thus, the claims are considered broad. The claims will therefore be evaluated based upon *in vivo* use of the oligonucleotide.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art

without undue experimentation (United States v. Telectronics, Inc., 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather a conclusion reached by many factors. These factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in In Re Wands (see above).

The state of the art at the time the application was filed and currently as exemplified by Lipford et al. (Immunology, 101:46-52, 2000) teaches that poly-guanosine motifs co-stimulate antigen-reactive CD8 T cells. Lipford teaches that G quartet structures may be involved in T-cell stimulation, because at least four, but not less than four consecutive G bases are conditional for stimulation (page 51). Furthermore, Mempel et al. (Immunology Letters 89, 2003, 47-57) teaches, "poly-G-oligodeoxynucleotides does not augment the naturally induced antitumoral CD8-T-cell response in P815 mastocytomas."

The applicant contemplates a genus of poly G motifs to co-stimulate cytotoxic T-lymphocytes (CTLs) or natural killer cells (abstract). The instant claims are directed to using a genus of oligonucleotides with a tumor specific antigen to treat a vertebrate subject having a tumor. The skilled artisan understands that the genus reads on antisense, aptamers, oligomer, etc. with a G motif. There is a variation among species embraced by the claimed genus. For example, the prior art teaches using G-rich oligo aptamers for inhibiting an immune response (WO 98/29430, cited on a PTO-1449). The instant specification does not specifically teach making and/or using a tumor specific antigen and an oligonucleotides 10-50 nucleotide long comprising a sequence chosen from GGGGG, GAGGG, GGGAG, GTGGG, and GGGTG, wherein the oligonucleotide does not comprise a CG dinucleotide to treat tumor in a subject. The applicant teaches an oligonucleotide (PZ2, SEQ ID NO: 2) with IL-2 co-stimulates T cells in

vitro (Example 7) and PZ2 co-stimulates natural killer cells in vitro (Example 8). The applicant further teaches that only single stranded PZ1 (SEQ ID NO: 1), PZ2 (SEQ ID NO: 2), and PZ3 (SEQ ID NO: 3), but not double stranded PZ1, PZ2, and PZ3 co-stimulate T cells in vitro. The applicant further teaches:

> To analyze the effects of ODN on T cells a costimulation assay was used. In this assay purified T cells are stimulated via their TCR (signal 1). This signal is not sufficient to induce cytokine secretion and subsequent T cell growth (see Figure 9A). Addition of exogenous IL-2 demonstrate that signal 1 is operative. ODN by itself have no stimulatory activity on T cells alone. If however T cells receive a signal via their TCR they become sensitive to ODN. ODN provide to these T cells a potent second signal that induces cytokine secretion (Figure 9B) and T cell growth (Figure 9A). The results demonstrate that G-motif ODN-costimulated anti-cD3 triggered T cells in a sequence and concentration dependent fashion. The analyses allowed the definition of the minimal ODN motif effective for T cell costimulation. Page 31.

With respect to tumor specific antigens, the prior art of record teaches that as tumor cells grow and die they produce tumor specific antigens (e.g., PSA). See Cancer Medicine: Section 2: Cancer Immunology in PubMed[online] Bethesda, MD USA: United States National Library of Medicine [retrieved on 27 December 2005]. Retrieved from: PubMed. The presence of antibodies to tumor specific antigens is already present in the subject. Tumors have evolved means to resist or hide from immune effector cells with tumor specific antigen. The effectiveness of using tumor specific antigens and genus of oligonucleotides for treating cancer in a patient is considered unpredictable.

The instant specification does not provide a working example of treating a tumor in a vertebrate subject using the method steps recited in the claimed invention. The prior art is absent for using a tumor specific antigen with an oligonucleotide 10-50 nucleotides long comprising a sequence chosen from GGGGG, GAGGG, GGGAG, GTGGG, GGGTG, wherein the oligonucleotide does not comprise a CG dinucleotide. The prior art has been directed to stimulating an immune response using an oligonucleotide comprising a CG dinucleotide. The applicant contemplates using the G motif as an adjuvant (page 6). As stated in the specification immune adjuvants are well known in the prior art (page 6). However, the relevance of this data to the treatment of tumors is unclear at best because neither the applicant nor the prior art provide a correlation or nexus between the obtained studies such as those provided by applicant with results the skilled artisan would reasonably expect to see for treating a tumor in a vertebrate subject using the claimed method. See Leitner et al., Current Pharmaceutical Design, 2001, 7:1641-67 and Mempel et al. (Immunology Letters 89, 2003, 47-57). Thus, the specification is not considered enabled for treating a tumor in a subject using the claimed method.

In conclusion, the instant specification and the claims coupled with the art of record, at the invention was made, do not provide sufficient guidance and/or evidence to reasonably enable the claimed invention. Given that oligonucleotides wherein a genus of oligonucleotides with a G motif is employed to treat a tumor in a vertebrate subject was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a anti-tumor effect produced by any oligonucleotide cited in the claims, one skilled in the art would have to engage in a large quantity of undue experimentation in order to practice the claimed invention based on the

applicants' disclosure and the unpredictability of treating a tumor using an oligonucleotide comprising a G motif.

Applicant's arguments filed 6/7/06 have been fully considered but they are not persuasive.

In response to applicant's argument that the working examples provided disclose such parameters as effective dosage and the mode of administration, so as to enable one of skill in the art to use the invention, the argument is not found persuasive because the specification does not provide a working example of the claimed method. "The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art." Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984). The instant specification and the prior art of record teach (see Leitner et al., Current Pharmaceutical Design, 2001, 7:1641-67, WO 98/29430, and Mempel et al. (Immunology Letters 89, 2003, 47-57)) the unpredictability of using the claimed genus of oligonucleotides in the instant invention. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Thus, it would require an undue amount of experimentation to practice the claimed method.

In response to applicant's argument that the fact that the working examples of the invention did not produce positive results in every assay tested does not mean that they are unpredictable because both positive data and negative data are consistent and statistically reliable, the argument is found persuasive because it is not apparent how in vitro results not using the material recited in the instant claims reasonably correlate to using the a genus of tumor

specific antigen with the claimed genus of oligonucleotides. In view of the lack of guidance in the specification, the skilled artisan would require undue experimentation to determine what oligonucleotides are considered enabled for use in the claimed method. See Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004).

In response to applicant's argument that at the time of filing of the present application, it was recognized in the art that specifically targeting tumor-specific antigens present in a subject constituted a potential means of cancer treatment (see Exhibits A-C), the argument is not found persuasive because while it is acknowledged that tumor specific antigens have been used in the prior art for stimulating an immune response in a subject with a tumor, neither the specification nor the prior art of record teach using a tumor specific antigen with a genus of oligonucleotides 10-50 nucleotide long comprising a sequence chosen from GGGGG, GAGGG, GGGAG, GTGGG, and GGGTG, wherein the oligonucleotide does not comprise a CG dinucleotide. The prior art (WO 98/29430) teaches that oligonucleotides embraced by the claimed genus would interfere with the immune response, resulting in depressing the immune response (which is undesired effect when using a tumor specific antigen). Furthermore, at the time of filing and currently Mempel et al. (supra) teach, "poly-G-oligodeoxynucleotides does not augment the naturally induced antitumoral CD8-T-cell response in P815 mastocytomas."

In response to applicant's argument that in view of examiner's comments (page 3, first paragraph), one of ordinary skill in the art would have no trouble appreciating that the observed increase in antigenicity is directly relevant to the ability of immune cells to attack tumor cells, i.e., treating the tumor, the argument is not found persuasive because upon further consideration the specification is not enabled because the instant specification does not provide a working

example of the claimed method. As stated above, the genus of oligonucleotides recited in the instant claims embrace oligonucleotides that would interfere with the subject's immune response. The specification and the prior art of record do not teach which species of poly G motifs would not interfere with the subject's immune response.

In response to applicant's argument that Example 7 indicates that G motif ODN act as adjuvants for generation of antigen-specific cytotoxic T cells in vivo and CTLs are important in tumor immunity, i.e., for killing tumor cells (See Abbas et al.), the argument is not found persuasive because example 7 discloses an oligonucleotide (PZ2, SEQ ID NO: 2) with IL-2 co-stimulates T cells in vitro. The instant claims do not require IL-2. In view of the prior art of record and lack of teaching in the specification for practicing the claimed method, example 7 is not recognized as correlating to the claimed method. In addition, example 7 is only limited to SEQ ID NO: 2.

In response to applicant's argument that Example 8 displays that G-motif (ODN PZ2) induced NK activity in vivo in experimental mice and NK cells are important in tumor immunity, i.e., for killing of tumor cells (See Abbas et al.), the argument is not found persuasive because the argument is not found persuasive because example 8 discloses an oligonucleotide (PZ2, SEQ ID NO: 2) co-stimulates natural killer cells with IL-2 in vitro. The instant claims do not require IL-2. In view of the prior art of record and lack of teaching in the specification for practicing the claimed method, example 7. In addition, example 7 is only limited to SEQ ID NO: 2 is not recognized as correlating to the claimed method.

In response to applicant's argument that Leitner (cited by the examiner to support enablement rejection) appears to be inapposite, the argument is not found persuasive because the

closest prior art, at the time of filing, is directed to using CG to stimulate an immune response and/or using G-rich aptamers for decreasing an immune response (WO 98/29430). Furthermore, at the time of filing and currently, poly-G-ODNs showed no enhance induction of an antitumoral CD8 response after in situ administration (Mempel et al., supra).

Response to Arguments

Applicant's arguments, see pages 8-9, filed 6/7/06, with respect to 112 second paragraph have been fully considered and are persuasive. The rejection of claim 114 has been withdrawn because the limitation is at the 3' terminus.

Applicant's arguments, see page 9, filed 6/7/06, with respect to 102(e) as anticipated by Krieg have been fully considered and are persuasive. The rejection of claims 107 and 108 has been withdrawn because the limitation in claims 107 and 108 is clearly defined in the specification (page 8 of original specification) and does not include CG dinucleotide.

Applicant's arguments, see page 9, filed 6/7/06, with respect to 102(b) as anticipated by Wagner have been fully considered and are persuasive. The rejection of claims 107 and 108 has been withdrawn because the limitation in claims 107 and 108 is clearly defined in the specification and does not include CG dinucleotide.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, SPE – Art Unit 1635, can be reached at (571) 272-4517.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman

BRIAN WHITEMAN
PATENT EXAMINER